F093 (cont)

In the E2 group NO concentrations on day 2 were significantly higher than on day 1 (37.3 ± 7.6 vs 21.4 ± 7.7 µmol/l); moreover, NO levels in the E2 group resulted significantly higher than in the placebo group on day 2 (37.3 ± 7.6 vs 22 ± 4.3 µmol/l), day 3 (47.5 ± 17.8 vs 18.2 ± 3.9 µmol/l), day 5 (40.7 ± 17.1 vs 19.2 ± 6.0 µmol/l), day 6 (38.1 ± 18.3 vs 20.0 ± 4.9 µmol/l) and day 7 (33.4 ± 5.2 vs 22.5 ± 5.7 µmol/l); the area under the curve of NO metabolites concentrations in the E2 group between day 1 and 8 was about 50% greater that in the placebo group. In conclusion, short-term transdermal E2 administration increases NO production in postmenopausal women; although long-term effects should be evaluated, our data suggest that a NO-mechanism could contribute to explain the cardiovascular protective effect of ERT in postmenopausal women.

F094

IMPROVED NITRIC OXIDE SYNTHESIS IN POSTMENOPAUSAL WOMEN TREATED WITH 17ß-ESTRADIOL VALERATE - EVIDENCE FOR RESPONDERS AND NON-RESPONDERS

B Imthurn, M Rosselli, A W Jäger#, R K Dubey*, P J Keller.
Clin. Endocrinology, Dep. of Obstet. and Gynecol., Univ. Hospital, Zurich; #Schering (Schweiz) AG, Zurich, Switzerland; *Clin. Pharm. Univ. Pittsburgh Med. Center, Pittsburgh PA, USA.

Increased incidence of cardiovascular disease in postmenopausal women (PMW) is related to ovarian dysfunction while hormone replacement therapy (HRT) has cardioprotective effects. Since atherosclerosis and hypertension is associated with impaired release of endothelium-derived nitric oxide (NO), we investigated whether HRT augments the levels of circulating NO.- Twenty-seven PMW received 2mg estradiol valerate per day orally for 21 days. Serum nitrite/nitrate (NO_2-/NO_3-) levels were assessed prior to initiation of HRT and after 12 months of treatment. Whereas the mean NO_2/NO_3- levels rised from 21.6±2.1µmol/L at baseline to 30.0±3.7µmol/L (p=0.005) after 12 months, this increase was significant (>30%; responders) in only 14 out of 27 PMW. In the remaining 13 PMW (non-responders) there was only a slight increase, no change or even a decrease in NO_2-/NO_3- levels. Furthermore, elevated NO_2/NO_3- levels in responders correlated with decreased serum LDL-C (low density lipoprotein) levels (r^2=0.154, p=0.038). - Our data suggest, that a considerable number, but not all PMW fully profit from the cardioprotective effects of HRT.

F095

THE VASORELAXANT EFFECT OF A SERIES OF ESTROGENIC AGONISTS AND PARTIAL AGONISTS IS NOT CORRELATED TO THEIR AFFINITY AT THE ESTROGEN RECEPTOR

M J Sheardown, S M Thorpe,
Endocrinology, Novo Nordisk, Novo Nordisk Park, 2760-DK Maaloev, Denmark

The relaxant effect of estrogen on precontracted vascular tissue is well known. In this study we have investigated the relaxant effects of 17-ß-estradiol, estrone, estriol and a series of estrogenic agonists and partial agonists in rings of rat thoracic aorta pre-contracted with 300 nM phenylephrine. The EC_{50} values for 17-ß-estradiol, estrone and estriol were 21, 250, and 58 μM, respectively. The potencies of the other compounds investigated were raloxifene (6), tarnoxifen (29), diethylstilbestrol (44) and 17-α-estradiol (160). The relaxant effect of 17-ß-estradiol was partly inhibited by the nitric oxide synthetase inhibitor L-NAME (100 μM) and was similarly reduced in rings denuded of endothelium. The effects of raloxifene and tamoxifen were greatly reduced in the presence of L-NAME. The affinity of these compounds for binding to the estrogen receptor was evaluated in competitive binding assays (competition with ^{3}H-17-ß-estradiol) in rabbit uterine cytosols using the classical dextran-coated charcoal (DCC) assay method. Interestingly there was no significant correlation between the potency in the rat aorta and the binding affinity (r^2 = 0.001, p > 0.93) suggesting this rapid relaxant effect is not mediated by the classical estrogen receptor. The data suggest that nitric oxide may be at least partly involved.

F096

LOW-DOSE HRT REDUCES VASCULAR RESISTANCE IN THE CENTRAL RETINAL ARTERY

W. M. van Baal, V. Mijatovic, C D A Stehouwer, J M G van Vugt, G A Dekker, H P van Geijn, E R A Peters-Muller, G A Voetberg, M J van der Mooren, P Kenemans.
Project "Ageing Women", Free University Hospital, De Boelelaan 1117, 1007 MB Amsterdam, The Netherlands.

Beneficial effects of HRT on the cardiovascular system in postmenopausal women are not fully explained by changes in plasma lipoproteins. Direct effects of oestrogens on vascular dynamics are also involved. Most studies have investigated effects of unopposed oestrogens. Effects on the central retinal artery (CRA), as a parameter of circulation in small arteries, have not been studied. In a prospective study we randomised 30 healthy postmenopausal women (mean age; 52 years) into two groups. Fifteen women were treated with orally 17ß-oestradiol 1 mg daily and dydrogesterone, 5 or 10 mg daily (day 15-28), and compared with 15 non-treated women. At baseline and after three months of therapy we measured vascular resistance (pulsatility index, PI) and flow of the CRA and of the uterine artery, using Color-Doppler ultrasound, as a parameter of arterial function. At baseline, vascular resistance parameters were positively correlated with time since menopause (CRA: rho=0.42; uterine artery: rho=0.50, P<0.05). After three months, the mean PI of the CRA decreased with 21% in the HRT group versus a 9% increase in the control group (P<0.01), and the mean PI of the uterine artery decreased with 17% in the HRT group versus a 10% increase in the control group (P=0.11). The mean minimum flow in the CRA and uterine artery increased with 31% (P<0.05) and 95% (P<0.05) whereas no changes in the control group were observed. It is concluded that short term oestrogen/progestagen therapy gives a significant decrease in vascular resistance of the CRA. Hormonal influences on this small artery have not been reported before.